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(54) Title: MICROEMULSIONS CONTAINING PHARMACEUTICAL COMPOSITIONS			
(57) Abstract Pharmaceutical compositions in the form of microemulsions comprise an oil, a mixture of high and low HLB surfactants in which the high HLB surfactant comprises an aliphatic, aryl or aliphatic-aryl sulfate, sulfonate or sulfosuccinate or salt thereof, an aqueous phase and a biologically active agent.			

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MICROEMULSIONS CONTAINING PHARMACEUTICAL COMPOSITIONS

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Field of the Invention

This invention relates to pharmaceutical compositions in the form of water-in-oil (w/o) self-emulsifying microemulsions, processes for their preparation and their use.

10 **Background of the Invention**

Microemulsions can be defined in general as thermodynamically stable, isotropically clear dispersions of two immiscible liquids stabilized by interfacial films of surface-active molecules. The formation of microemulsions usually involves a combination of three to five components, namely, an oil, water, a surfactant, a cosurfactant and an electrolyte.

15 The tendency to form either a water-in-oil (w/o) or an oil-in-water (o/w) microemulsion is influenced by the properties of the oil and the surfactant. Surfactants are conveniently classified on an empirical scale known as the hydrophilic-lipophilic balance (HLB) which runs from 1 to 45. In general, (w/o) microemulsions are formed using surfactants (or emulsifiers) which have an HLB value in the range of about 3 to 6 while (o/w)

20 microemulsions are formed using surfactants which have an HLB value in the range of about 8 to 18. It has long been recognized that low interfacial tension contributes to the thermodynamic stability of microemulsions. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases, and be preferentially absorbed at the water-oil interface with concomitant lowering of interfacial tension. When 25 interfacial tension is less than 2×10^{-2} dyn/cm, a stable microemulsion can form. General reviews of microemulsions are provided by Bhargava *et al.*, Pharm. Tech., 46-53, March 1987 and Kahlweit, Science, 240, 617-621, 1988.

30 Microemulsions are typically substantially non-opaque, that is they are transparent or opalescent when viewed by optical microscopic means. In the undisturbed state, they are optically isotropic (non-birefringent) when examined under polarized light. The dispersed phase typically comprises particles or droplets which are normally between 5 and 200 nm in size and this gives rise to their optical transparency. These particles may be spherical although other structures are feasible.

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The role of the cosurfactant, usually a short-chain alcohol, is to increase the interfacial fluidity by penetrating the surfactant film and consequently creating a disordered film due to the void space among surfactant molecules. The use of a cosurfactant in microemulsions is however optional and alcohol-free self-emulsifying emulsions and

microemulsions have been described in the literature (see for instance, Pouton *et al.*, *Int. Journal of Pharmaceutics*, 27, 335-348, 1985 and Osborne *et al.*, *J. Disp. Sci. Tech.*, 9, 415-423, 1988).

- 5 There are many advantages to the use of a microemulsion over a conventional emulsion (or macroemulsion) for drug transport (delivery). Microemulsions form spontaneously, without the need for a high input of energy and are therefore easy to prepare and scale up for commercial applications; they have thermodynamic stability due to their small particle size and therefore have a long shelf life; they have an isotropically clear appearance so that
- 10 they may be monitored by spectroscopic means; they have a relatively low viscosity and are therefore easy to transport and mix; they have a large interfacial area which accelerates surface reactions; they have a low interfacial tension which permits flexible and high penetrating power and, lastly, they offer the possibility of improved drug solubilization and protection against enzymatic hydrolysis. In addition, microemulsions may undergo
- 15 phase inversion upon addition of an excess of the dispersed phase or in response to a temperature change and this is a property of these systems that can affect drug release from microemulsions both *in vitro* and *in vivo*. The reasons for this improved drug delivery are not however well understood.
- 20 The use of lipid-based microemulsions to enhance the bioavailability of different drugs, including peptides, has already been proposed. Thus, GB 2 222 770-A (Sandoz Ltd) describes microemulsions and corresponding microemulsion "pre-concentrates" for use with the highly hydrophobic cyclosporin peptides. Thus, a suitable pre-concentrate comprises 1,2-propylene glycol as the hydrophilic component, a caprylic-capric acid
- 25 triglyceride as the lipophilic component and a mixture of a polyoxyethylene glycolated hydrogenated castor oil and glycerin monooleate (ratio 11:1) as the surfactant-cosurfactant. Such formulations may then be diluted with water, to give oil-in-water rather than water-in-oil microemulsions.
- 30 GB 2 098 865A (Sandoz Ltd) describes topical compositions in the form of microemulsions comprising a water-immiscible organic solvent, an emulsifier, a co-emulsifier, water and a (non-peptide) therapeutic agent. These formulations are said to have improved skin penetrating properties. Suitable organic solvents include mono- or diesters of glycerol with a (C₆-22) carboxylic acid, such as glyceryl caprylate (which may
- 35 also act as a co-emulsifier).

US 4 712 239 (Muller *et al.*) describes multi-component systems for pharmaceutical use comprising an oil, a nonionic surfactant with an HLB value above 8 and a co-surfactant which is a partial ether or ester of a polyhydroxyl alcohol and a (C₆-22) fatty alcohol or

acid, which components form a "single phase" on mixing. The special properties of the system are attributed to the particular blend of surfactant and co-surfactant selected. An aqueous phase is an optional extra and the therapeutic agent may be lipophilic or hydrophilic. Such systems are said to give enhanced transdermal delivery characteristics.

5 Amongst the examples provided, one (example 1, formulation I) has PEG 20-ethylene oxide (20 EO)-oleic acid glycerol partial esters (40%), caprylic-capric acid glycerol partial esters (42%), monoglyceride (24%), medium-chain triglycerides (16%) and water (20%).

10 GB 1 171 125 (Glaxo Laboratories Ltd.) describes microemulsions comprising a hydrophilic oil, a blend of low and high HLB surfactants and an aqueous phase, for use as injectable preparations. In particular, example 15 thereof contains in the lipophilic phase a mixture of coconut oil and sorbitan monooleate. The patent is concerned with improved formulations and is silent on bioavailability.

15 WO 88/00059 (Engström *et al.*, and the corresponding paper, *J. Dispersion Sci. Technol.*, 11, 479, 1990) discloses controlled release compositions for biologically active materials comprising an "L2-phase" and containing an unsaturated (C₁₆₋₂₂)-fatty acyl monoglyceride and an unsaturated (C₁₆₋₂₂)-fatty acyl triglyceride, in a ratio of from 1:1 to 3:1, and a polar liquid such as water. Such an unsaturated (C₁₆₋₂₂)-fatty acyl monoglyceride is a low HLB surfactant. There is, however, no mention of the additional inclusion of a high HLB surfactant. The existence of an L2 phase had previously been described for a water/mono-caprylin/tricaprylin system by Friberg *et al.*, *J. Amer. Oil Chem. Soc.*, 47, 149, 1970. Again, there is no mention of the additional inclusion of a high HLB surfactant.

20 25 Physical studies have been reported on systems comprising the triglyceride trioctanoin, in combination with the medium-chain fatty acid octanoic acid and the sodium salt thereof (Friberg, S *et al.*, *Chem. Phys. Lipids*, 6, 364-372, 1971). Such systems however did not contain water or a low HLB surfactant. In addition, physical studies have also been 30 reported on formulations comprising sodium octanoate and water in octanoic acid and which concentrate on the L-2 phase (Ekwall, P, *Colloid and Polymer Sci.*, 266, 184-191, 279-282, 721-728, 729-733, 1150-1160, 1161-1173 and 267, 607-621, 1989).

35 Hayashi *et al* have reported that the medium-chain fatty acid salts, sodium caprylate and sodium caprate have an enhanced effect *per se* on colonic drug absorption (*Pharm. Res.*, 9, 648-53, 1992; 8, 1365-71, 1991; 6, 341-6, 1988; and 5, 786-9, 1988).

Dioctyl sodium sulfosuccinate (DSS) better known as Docusate Sodium or Aerosol OT is widely used as a solubilizing, wetting, emulsifying or dispersing agent. Known

pharmaceutical uses of DSS include: a) as a therapeutic agent, alone or as an adjuvant in the prevention or treatment of constipation, b) as a tablet formulation adjuvant to facilitate tablet coating and improve tablet disintegration and dissolution characteristics, and c) as an absorption enhancer. DSS has been reported to increase the small intestinal absorption of 5 heparin (Engel, R.H. *et al.*; J. Pharm. Sci. 58, 706-710, 1969), insulin (Dupont, A. *et al.*; Ugeskrift Lager 119, 1461-1463, 1957) and phenolsulfonphthalein (Khalaffalah, N. *et al.*; J. Pharm. Sci. 64, 991-994, 1975).

Microemulsions as topical drug delivery vehicles formed by the system
10 water/octanol/dioctyl sulfosuccinate have been reported by Osborne, D.W. *et al.*; (Drug Dev. Ind. Pharm. 14, 1203-1219, 1988; J. Pharm. Pharmacol. 43, 451-454, 1991). These studies have shown that *in vitro* transdermal flux of hydrophilic drugs is highly dependent upon the composition of microemulsion, particularly on the octanol/DSS ratio. *In vitro* release of lipophilic drugs from oil-in-water microemulsions consisting of 15 isopropyl myristate (oil), 1-butanol, (co-surfactant), dioctyl sodium sulfosuccinate and water/buffer have been described by Trotta, M. *et al.*; (J. Control. Rel. 10, 237-243, 1989; Acta Pharm. Technol. 36, 226-231, 1990).

EP-387647 (Matouschek, R.) describes pharmaceutical microemulsion compositions
20 containing acidic or basic drug and compound forming ion-pairs for nasal, rectal or transdermal delivery. Suitable oils included isopropyl myristate, 2-octyl dodecanol and paraffin oil with the surfactant comprising polyoxyethylene fatty acid ester and/or polyoxyethylene fatty alcohol ether. The cosurfactant used was polyoxyethylene glycerol fatty acid ester with water being the aqueous phase. In the case of basic drugs the 25 compound forming ion-pair was sulphate.

Pharmaceutical microemulsion compositions which have improved solubility, stability and/or particle size for the oral delivery of therapeutic agents, in particular for peptides, is still needed. We have now surprisingly found that further improved drug delivery 30 characteristics may be obtained with (w/o) microemulsions by the further modification of the surfactant system.

Summary of the Invention

Accordingly, the present invention provides a pharmaceutical composition comprising:
35 (a) an oil;
(b) a surfactant system comprising a mixture of high and low HLB surfactants in which the low HLB surfactant is an admixture of:
i) a medium-chain or long chain free fatty acid; and

ii) a medium or long chain mono/di-glyceride or a sorbitan medium or long chain ester or mixtures thereof;

and the high HLB surfactant is:

iii) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;

iv) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;

v) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or

vi) a mixture of any of iii), and/or iv), and/or v) above; and

wherein the high HLB surfactant is optionally mixed with the salt of a medium or long chain fatty acid and/or a nonionic high HLB surfactant;

(c) an aqueous hydrophilic phase; and

(d) a water-soluble biologically active agent;

which on admixing form a stable, self-emulsifying, water-in-oil (w/o) microemulsion.

Brief Description of the Drawings

Figure 1 illustrates a pseudo-ternary phase diagram of a system comprising (1) an oil and a second low HLB surfactant in a fixed ratio X, (2) an aqueous phase and (3) a free fatty acid and dioctyl sodium sulfosuccinate in a fixed ratio Y;

Figure 2 illustrates a pseudo-ternary phase diagram of the system comprising CAPTEX 8000 and CAPMUL C8 (ratio 2:1), caprylic acid and dioctyl sodium sulfosuccinate (pure 100%, USP) (ratio 3:1) and deionized water.

25 Figure 3 illustrates a pseudo-ternary phase diagram of the system comprising CAPTEX 8000 and CAPMUL C8 (ratio 2:1), caprylic acid and dioctyl sodium sulfosuccinate (85% surfactant, 15% sodium benzoate) (ratio 3:1) and deionized water.

Figure 4 illustrates a pseudo-ternary phase diagram of the system comprising MIGLYOL 808 and Imwitor 308 (ratio 2:1), caprylic acid and dioctyl sodium sulfosuccinate (pure 100%, USP) (ratio 3:1) and deionized water.

Figure 5 illustrates a pseudo-ternary phase diagram of the system comprising MIGLYOL 808 and Imwitor 308 (ratio 2:1), caprylic acid and dioctyl sodium sulfosuccinate (ratio 3:1) and saline.

35 Detailed Description of the Invention

The microemulsions of the present invention without a biologically therapeutic drug are novel and useful as precursors to drug-containing microemulsions. Accordingly, the present invention provides for a pharmaceutical composition comprising:

(a) an oil;

(b) a surfactant system comprising a mixture of high and low HLB surfactants in which the low HLB surfactant is an admixture of:

- i) a medium-chain or long chain free fatty acid; and
- ii) a medium or long chain mono/di-glyceride or a sorbitan medium or long chain ester or mixtures thereof;

5 and the high HLB surfactant is:

- iii) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;
- iv) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;
- 10 v) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or
- vi) a mixture of any of iii), and/or iv), and/or v) above; and

15 15 wherein the high HLB surfactant is optionally mixed with the salt of a medium or long chain fatty acid and/or a nonionic high HLB surfactant; and

(c) an aqueous hydrophilic phase.

20 In a further aspect the present invention provides for a pharmaceutically acceptable, stable, self-emulsifying microemulsion comprising each of (a), (b) and (c) above and (d) a water-soluble biologically active agent, which on admixing form a stable, self-emulsifying, water-in-oil (w/o) microemulsion.

25 The inclusion in a microemulsion of an aliphatic, preferably a medium-chain salt of alkyl or dialkyl sulfates or sulfonates or sulfosuccinates, has unexpectedly been found to further enhance the absorption of a biologically active agent when administered in formulations according to the invention.

30 It will be appreciated by the skilled man that the oil and the low HLB surfactant will together form a continuous lipophilic phase.

In a preferred embodiment of the invention the pharmaceutically acceptable, stable, self-emulsifying microemulsion comprises:

- (a) an oil;
- 35 (b) a surfactant system comprising a mixture of high and low HLB surfactants in which the low HLB surfactant is an admixture of
 - i) a medium-chain free fatty acid; and
 - ii) a medium chain mono or di-glyceride, or mixtures thereof;and in which the high HLB surfactant is:

- iii) a medium chain alkyl or dialkyl sulfate or pharmaceutically acceptable salt thereof;
- iv) a medium chain alkyl or dialkyl sulfonate or pharmaceutically acceptable salt thereof;
- 5 v) a medium chain alkyl or dialkyl sulfosuccinate or pharmaceutically acceptable salt thereof; or
- iv) a mixture of any of iii), and/or iv), and/or v) above; and

wherein the high HLB surfactant is optionally mixed with the salt of a medium chain fatty acid and/or a nonionic high HLB surfactant;

- 10 (c) an aqueous hydrophilic phase; and
- (d) a water-soluble biologically active agent;

which on admixing form a stable, self-emulsifying, water-in-oil (w/o) microemulsion.

The preferred surfactant system comprises a mixture of both high and low HLB

- 15 surfactants in which the high HLB surfactant is a medium chain fatty alkyl or di-alkyl sulfate, sulfonate or sulfosuccinate, or a pharmaceutically acceptable salt thereof, preferably the salt, and the high HLB is optionally admixed with a medium-chain fatty acid salt and/or may be optionally admixed with a high HLB surfactant which is non-ionic in character. Preferably the high HLB surfactant is admixed with a pharmaceutically
- 20 acceptable salt of a medium chain fatty acid. Preferably, the second low HLB surfactant is a medium chain mono- or di-glyceride or a mixture thereof.

The chain lengths of the high and low HLB surfactants used in the microemulsion need not be the same length. For example, the medium chain fatty acid may be 8 carbons, and

- 25 the medium chain fatty acid salt may be of 10 carbons.

The term "medium-chain", such as used in the term "medium-chain fatty acid" or "medium chain alkyl or dialkyl", and as used herein refers to a carbon chain, which may be saturated, mono-unsaturated or poly-unsaturated, having from 6 to 12, preferably from 8

- 30 to 10 carbon atoms, which may be branched or unbranched, preferably unbranched, and in which fatty acyl chain may be optionally substituted. Optional substituents include for instance, halogen, hydroxy, alkoxy, thioalkyl or halo substituted alkyl. Halogen, as used herein includes F, Cl, Br and I.

35 The term "long-chain", such as used in the term "long-chain fatty acid" or "long chain alkyl or dialkyl", as used herein refers to a carbon chain, which may be saturated, mono-unsaturated or poly-unsaturated, having from 14 to 22, preferably 14 to 18, carbon atoms which may be branched or unbranched, preferably unbranched, and which may be optionally substituted as noted above for "medium chain".

5 Suitable oils for use in the oil or lipophilic phase will be pharmaceutically acceptable and include fatty acid triglycerides (fatty acid triesters of glycerol), fatty acid diesters of propylene glycol, and/or polyol esters or mixtures thereof. The fatty acid moieties may be medium-chain or long-chain moieties or mixtures thereof.

10 As used herein, the term "polyol", such as used in the term "medium chain polyol esters" in the lipophilic phase, is a compound which contains one or more ester linkages derived from a polyhydric alcohol, i.e. a carbon backbone containing two or more hydroxyl groups. Such carbon backbones for making such esters include but not limited to, ethylene glycol, propylene glycol or polyethylene glycol (PEG). PEG is also referred to as a polyglycol with ethylene glycol as a polymerized unit. Preferably, the polyol is propylene glycol or a polyethylene glycol.

15 20 Suitable fatty acid triglycerides and fatty acid diesters of propylene glycol for use in the present invention may be of natural, semi-synthetic or synthetic origin and may include blends of different fatty acid triglycerides and/or fatty acid diesters of propylene glycol or other polyol esters. Such blends include not only physical blends of medium- and long-chain fatty acid triglycerides and/or diesters but also triglycerides and/or diesters which have been chemically modified, by, for instance, interesterification, to include a mixture of medium- and long-chain fatty acid moieties. Suitable such triglycerides and diesters are readily available from commercial suppliers.

25 30 Additionally, such suitable lipophilic phase medium chain esters for use herein may also include those which are polyethylene based. Such examples for propylene glycol and polyethylene based include those available under the trade names MYRITOL; CAPTEX (Karlshams Lipid Specialties, Columbus OH), for instance CAPTEX 200; MIGLYOL (BASF), for instance the grades MIGLYOL 840; SOFITIGEN (Huls America Inc., Piscataway NJ), for instance SOFTIGEN 767; LABRAFAC and LABRASOL (Gattefosse Corp., Westwood, NJ), for instance LABRAFAC CM-10. Propylene glycol examples are CAPTEX 200 and Miglyol 840 are propylene glycol dicaprylate/dicaprate systems. PEG based systems are Softigen, which is a PEG-6 Caprylic/Capric Glyceride system; LABRAFAC CM-10 are the glycerol and PEG esters of C₈ and C₁₀ fatty acids, and LABRASOL is a PEG-8 Caprylate/Caprate glyceride ester system.

35 For preferred medium-chain fatty acid triglycerides, the fatty acid composition comprises caprylic (C₈) acid optionally admixed with capric (C₁₀) acid, for instance from 50 to 100% (w/w) of caprylic acid and from 0 to 50% (w/w) of capric acid triglycerides. Suitable examples include those available under the trade names MYRITOL; CAPTEX

(Karlshams Lipid Specialties, Columbus OH), for instance CAPTEX 300, CAPTEX 350, CAPTEX 355, CAPTEX 850 and CAPTEX 8000; MIGLYOL (BASF), for instance the grades MIGLYOL 808, MIGLYOL 810, MIGLYOL 812 and MIGLYOL 818 (which also comprises a linoleic acid triglyceride) and MAZOL 1400 (Mazer Chemical, Gurnee, IL).

5 The fatty acid content of representative products is given in the following table (manufacturer's data); C₆ and C₁₂ represent caproyl and lauroyl fatty acyl chains, respectively.

Product	Caprylic %	Capric %	Other %
CAPTEX 355	55	42	C ₆ , 2
CAPTEX 8000	98.5	<1	<1
MIGLYOL 808	>99%		
MIGLYOL 810	65-75	25-35	C ₆ , 2
MIGLYOL 812	50-60	30-45	C ₆ , 2, C ₁₂ , 5

10 Suitable long-chain fatty acid triglycerides may be conveniently obtained from neutral plant, vegetable and fish oils such as shark oil, coconut oil, palm oil, olive oil, sesame oil, peanut oil, castor oil, safflower oil, sunflower oil and soybean oil, which oils may be in their natural state or partially or fully hydrogenated. Soybean oil consists of oleic acid (25%), linoleic acid (54%), linolenic acid (6%), palmitic acid (11%) and stearic acid (4%)

15 triglycerides while safflower oil consists of oleic acid (13%), linoleic acid (76%), stearic acid (4%) and palmitic acid (5%) triglycerides. Suitably in such long-chain fatty acid triglycerides, the major fatty acid components are C₁₈-saturated, monounsaturated or polyunsaturated fatty acids, preferably C₁₈-monounsaturated or polyunsaturated fatty acids, such as oleic, linoleic and linolenic acid.

20 Other suitable triglycerides include interesterified triglycerides which may be derived synthetically by chemically reacting blends of medium- and long-chain triglycerides, for instance triglycerides containing caprylic and capric acid moieties and vegetable oils rich in oleic or linoleic acids. Examples of suitable such interesterified triglycerides include the

25 products available from Karlshams Lipid Specialties, as CAPTEX 810A - D and 910A - D, which typically contain from 30 to 80% capric and caprylic acids, 10 to 50% linoleic acid (810 series) or 10 to 60% oleic acid plus up to 5% linoleic acid (910 series), and up to 25% of other acids.

30 Suitable fatty acid diesters of propylene glycol include medium- and long-chain fatty acid diesters. Preferably the diester is formed from medium-chain fatty acids, more preferably

from caprylic and capric acids, most preferably from caprylic acid. Preferred diesters comprise from about 50 to 100% caprylic acid and from 0 to 50% capric acid. A suitable thereof is the product CAPTEX 200 (Karlshams Lipid Specialties) which comprises caprylic acid (68%), capric acid (27%) and caproic acid (4%) (manufacturers data).

5

The high HLB surfactant for use in the present invention is an aliphatic, aryl or an aliphatic-aryl sulfate, sulfonate or sulfosuccinate. The aliphatic moiety is a medium or long chain alkyl or dialkyl group. The medium chain moiety contains C₆ to 12, preferably 8 to 10 carbons, and the long chain moiety contains from C₁₄ to 24, preferably 14 to 18 carbons as previously defined. The aliphatic chain may be branched or unbranched and may be optionally substituted and may be saturated, mono-unsaturated or poly-unsaturated. Preferably the aliphatic moiety is of medium chain length.

There are two forms of linkages possible with the sulfate, sulfonate and sulfosuccinate groups herein, one is designated as a fatty acyl ester linkage and the other an ester linkage. If the aliphatic or aryl moiety forms a fatty acyl ester linkage with the sulfate, sulfonate or sulfosuccinate, i.e. contains an additional carbonyl [C(O)] group, the aliphatic (or aryl) group becomes known as the fatty acid portion of the ester linkage. A fatty acyl ester linkage, is for instance, a C₆-12-C(O)-O S(O)₃Na⁺. This is in contrast to the generally recognized linkage of C₆-12-C-O-S(O)₃Na⁺, referred to herein as the ester linkage. This terminology stems from the reaction of a C₆-12-OH moiety with the sulfonic acid O-S(O)₂⁻ Na⁺ group forming a sulfonic ester. Preferably the linkage is an ester linkage and not a fatty acyl ester linkage. More preferably the linking group is a medium chain alkyl or dialkyl moiety.

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As used herein the term "aryl" sulfate, sulfonate or sulfosuccinate means a phenyl or naphthyl moiety which may be optionally substituted. Suitable aryl sulfonates include, for instance, benzene sulfate or sulfonate, naphthylsulfate or sulfonate.

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As more than one site for attachment is possible with the sulfates, sulfonates and sulfosuccinates they may be mixtures of both aliphatic and aryl linkages formed, such as dodecyl or lauryl benzene sulfate or sulfonate or sulfosuccinate. This combination as used herein is referred to as "aliphatic-aryl". Preferably the aliphatic moiety in this instance is a medium chain alkyl or dialkyl group.

35

Suitable long chain alkyl or dialkyl sulfates, sulfonates and sulfosuccinates include, but are not limited to myristic (C₁₄), palmitic (C₁₆), palmitoleic (C₁₆:1), stearic (C₁₈), oleic (C₁₈:1), vaceenic (trans oleic acid) or linoleic (C₁₈:2). Suitably, the alkyl and dialkyl

moieties may be mixtures of different medium and long chain moieties, such as a dialkyl sulfate having a C12 and a C16 group.

Preferably the sulfates, sulfonates and sulfosuccinates are medium chain alkyl or dialkyl

5 derivatives. Suitable medium chain moieties include, but are not limited to octyl (C₈), decyl (C₁₀), dodecyl (C₁₂), iso-octanoyl, or di-octyl, di-decyl, or di-dodecyl.

Preferably, the medium chain moiety is octyl, decyl, dodecyl, or dioctyl. More

preferably, the high HLB is a octyl, decyl, dodecyl or di-octyl sulfosuccinate, or is a octyl, decyl, or dodecyl sulfate.

10

Yet another aspect of the instant invention is the combination of mixtures of the different aliphatic, aryl or aliphatic-aryl sulfates, sulfonates and sulfosuccinates as the high HLB surfactant used herein.

15

Suitably, the sulfates, sulfonates, or sulfosuccinates will be pharmaceutically acceptable water-soluble salts, for instance alkali metal salts, such as sodium and potassium salts, or ammonium or quaternary ammonium salts also referred to as N(R)₄ wherein R is an alkyl derivative, or is a primary and secondary (protonated) amine salt, such as ethanolamine or triethanolamine. Preferably, the salts are the alkali metal salts. Suitably, the salts are of

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the medium chain alkyl or dialkyl sulfates, such as octyl, decyl or dodecyl sulfate; or the salts of dialkyl sulfosuccinate, of which the salts sodium dioctyl sulfosuccinate and sodium dodecyl sulfate are preferred. Sodium dioctyl sulfosuccinate (DSS) and sodium dodecyl sulfate (SDS) have estimated HLB values of 41 and 40 respectively.

25

Suitable medium-chain free fatty acids for use in the present invention include caprylic (C₈), capric (C₁₀), and lauric (C₁₂) acids, and mixtures thereof. Preferred free fatty acids are caprylic and capric, and most preferred is caprylic. Preferred salts of the medium chain fatty acids are the alkali metal salts, such as sodium or potassium.

30

Preferred medium chain fatty acids salts are sodium caprylate and sodium caprate with an estimated HLB value of 23 and 21, respectively. Most preferred medium chain fatty acid salt is sodium caprylate.

Suitably, the ratio of free medium fatty acid to the total, by weight, high HLB surfactants is in the range of from about 10:1 to 1:1, more suitably from about 4:1 to 1:1.

35

Preferably, the surfactant system also comprises in addition to the first low HLB surfactant (the free fatty acid), a further (second) low HLB surfactant, such as a medium or long chain fatty acid monoglyceride, a medium or long chain fatty acid diglyceride, a mixture of said mono- and di-glycerides, or a sorbitan medium-chain ester. Preferably

the second low HLB surfactant is a medium chain mono- or di-glyceride or a mixture thereof.

Suitably the ratio of the first low HLB, the free fatty acid, to the second low HLB surfactant is 10:1 to 1:10. Preferably, the ratio is from 5:1 to 1:5, and most preferably from 3:1 to 1:1.

Suitable non-ionic high HLB surfactants for the present invention include, but are not limited to:

- 10 (a) polyoxyethylene fatty acyl esters, for example polyoxyethylene stearic acid esters of the type available under the trade name MYRJ (ICI Americas, Inc.), for instance the product MYRJ 52 (a polyoxyethylene 40 stearate);
(b) polyoxyethylen-sorbitan fatty acid esters (polysorbates), for example the mono- and tri-lauryl, palmityl, stearyl and oleyl esters, for instance the polyoxyethylene sorbitan monooleates available under the trade name of TWEEN (ICI Americas Inc.), such as TWEEN 20, 21, 40, 60, 61, 65, 80, 81 and 85, of which class TWEEN 80 is especially preferred;
- 15 (c) PEG glycerol ethers, such as the polyethylene glycol long-chain alkyl ethers, which include polyethylated glycol lauryl ether; and PEG fatty alcohol ethers; and
- 20 (d) PEG glycerol esters and PEG glycol fatty acid esters, such as the long-chain alkyl esters, which include PEG-monostearate;

For use herein, the non-ionic high HLB surfactant preferably has an HLB value in the range of 13 to 20.

25 In microemulsions of the present invention, a non-ionic high HLB surfactant may be usefully be included as an auxiliary high HLB surfactant to produce microemulsions which can solubilize a larger amount of aqueous phase. Such microemulsions are, however, generally comparatively more viscous than those in which the non-ionic high HLB surfactant is absent.

30 Suitably, the amount of high HLB surfactant (aliphatic, aryl or aliphatic-aryl sulfate, or sulfonates, or sulfosuccinates) to any additional high HLB surfactant, (such as the fatty acid salt and/or the non-ionic high HLB surfactant) is about 10% to less than 100% (w/w) of the total amount of high HLB surfactant. Preferably, from about 50 to 100% (w/w) and most preferably from 80% to 100% (w/w).

35 The second low HLB surfactant, is suitably, a fatty acid monoglyceride, fatty acid diglyceride, a mixture of mono- and di-glycerides or a sorbitan medium or long-chain fatty

acid ester, as well as mixtures of any of these low HLB surfactants thereof. Suitable mono- and di-glycerides may each include blends of different fatty acid mono- and di-glycerides and the fatty acid moieties may be of medium- or long-chain length or they may be a mixture thereof. Preferably the second low HLB surfactant is a fatty acid monoglyceride, as hereinbefore defined.

The surfactant system may additionally contain other surfactants, such as, but not limited to:

- 5 i) other lipids, such as phospholipids which may be anionic, cationic or zwitterionic, in particular lecithins, such as soya lecithins, egg lecithin or egg phosphatide, cholesterol or long-chain free fatty acids such as oleic acid;
- 10 ii) anionic surfactants, such as bile salts and the alkali metal salts thereof, including, but not limited to cholate, deoxycholate, etc., sodium taurocholate and C₆-C₁₈ fatty acyl carnitines.
- 15 iii) cationic surfactants, such as cetyl ammonium bromide (CTAB) or benzalkonium bromide.

Suitable medium chain fatty acid mono- and di-glycerides are formed from caprylic and capric acids. Suitable blends comprise from about 50 to 100% caprylic acid and from 0 to 50% capric acid. Mixtures of mono-and di-glycerides preferably comprise at least 50, 20 more preferably at least 70% by weight of monoglycerides. Suitable commercial sources of these include the products available under the trade name CAPMUL (Karlsham Lipid Specialties), for instance the products CAPMUL MCM which comprises monoglycerides (77%), diglycerides (21%) and free glycerol (1.6%), with a fatty acid composition which comprises caproic acid (3%), caprylic acid (67%) and capric acid (30%) and CAPMUL 25 C₈ which has monoglycerides (70 - 90%), diglycerides (10 - 30%) and free glycerol (2 - 4%), with a fatty acid composition which comprises at least 98% caprylic acid (manufacturer's data expressed as oleates; actual C₈/10 mono- and diglyceride content of about 45%, respectively).

In a preferred embodiment of the present invention, the low HLB surfactant contains a 30 mixture of mono- and diglycerides having at least about 80% by weight, preferably at least about 90% by weight, and more preferably at least about 95% by weight of a caproic, caprylic, capric monoglyceride or mixtures thereof, preferably a caproic, caprylic, capric monoglyceride or mixtures thereof, more preferably a caprylic, capric monoglyceride or mixtures thereof. Commercial examples of these surfactants include Imwitor 308 (Huls 35 America, Inc.) which has about 80-90% wt. caprylic monoglycerides; and Glycerol Monocaprylin, manufactured as 1-monoctanoyl-rac-glycerol (Sigma Chemicals) having about 99% wt. caprylic monoglycerides; and Glycerol Monocaprate, manufactured as 1-monodecanoyl-rac-glycerol (Sigma Chemicals) having about 99% wt. capric mono-glycerides.

Suitable long-chain fatty acid monoglycerides include glycerol monooleate, glycerol monopalmitate and glycerol monostearate. Suitable commercially available examples of such include the products available under the trade names MYVEROL, such as

- 5 MYVEROL 18-92 (a sunflower oil monoglyceride) and 18-99 (a rapeseed oil monoglyceride), MYVATEX and MYVALPEX, respectively, from Eastman Kodak Chemicals, Rochester, New York. A further useful long-chain fatty acyl monoglyceride-containing product is ARLACEL 186 (available from ICI Americas Inc.) which includes, in addition to glycerol monooleate, propylene glycol (10%). The main fatty acids of
- 10 MYVEROL 18-92 are oleic acid (19%), linoleic acid (68%) and palmitic acid (7%) while those of MYVEROL 18-99 are oleic acid (61%), linoleic acid (21%), linolenic acid (9%) and palmitic acid (4%). Suitably, in such long-chain monoglycerides, the major fatty acid component is a C₁₈-saturated, monounsaturated or polyunsaturated fatty acid, preferably a C₁₈-mono-unsaturated or polyunsaturated fatty acid. In addition, diacetylated and
- 15 disuccinylated versions of the monoglycerides such as the product available under the trade name Myvatex SMG are also useful.

Suitable sorbitan long-chain esters for use in the present invention include sorbitan monooleate, available commercially under the trade names SPAN 80 and ARLACEL 80

- 20 and sorbitan sesquioleate, available commercially under the trade names SPAN 83 and ARLACEL 83. Suitable sorbitan medium-chain esters for use in the present invention include sorbitan caprylate, sorbitan caprate, sorbitan laurate.

Suitably, the HLB of the primary and secondary low HLB surfactant will have an average

- 25 HLB value in the range of about 2 to 8. The HLB values of the products CAPMUL MCM, MYVEROL 18-99, ARLACEL 80, ARLACEL 83 and ARLACEL 186 are respectively about 5.5 to 6, 3.7, 4.3, 3.7 and 2.8 while the HLB of caprylic and capric acids are 5.8 and 4.8 respectively. The estimated HLB of 1-monocaprylin is about 8.0.

- 30 In a preferred embodiment of the present invention, microemulsions comprise medium-chain fatty acid components, such as those derived from caprylic and capric acids, especially those derived from caprylic acid. Accordingly, preferred microemulsions include blends of CAPTEX 355, 810, CAPTEX 8000 or CAPTEX 200, particularly CAPTEX 8000; CAPMUL MCM or CAPMUL C₈, particularly CAPMUL C₈; and
- 35 caprylic acid/sodium caprylate and/or capric acid/sodium caprate, particularly caprylic acid/sodium caprylate.

As used herein, the term "therapeutic agent" or "biologically active material" refers not only compounds which have use as therapeutic and/or prophylactic agents (hereinafter also

referred to as "drugs") but also compounds which may be of use as diagnostic agents. Such materials will be soluble in the hydrophilic phase and have an HLB value of at least that of the high HLB surfactant(s) used in the formulation, to ensure that the drug is preferentially dissolved in the hydrophilic rather than the lipophilic phase. Such materials 5 include both peptides and non-peptides. Suitable peptides include not only small peptides but also larger peptides/polypeptides and proteins. Suitable such peptides preferably have a molecular weight from about 100 to 10,000, more preferably from about 100 to about 6,000. Especially preferred are peptides having from 2 to 35 amino acid moieties. Higher molecular weight peptides, even those with a molecular weight of above 10,000, 10 up to about 50,000, may also be accommodated in microemulsions of the present invention.

Suitable small peptides have from about 2 to about 10, more preferably from about 2 to about 6 amino acid moieties. Preferred small peptides include the fibrinogen receptor antagonists (RGD containing peptides) which are tetrapeptides with an average molecular 15 weight of about 600. These peptide antagonists are highly potent platelet aggregation inhibitors at plasma levels as low as 1 pmol/ml. Preferred fibrinogen antagonists include the peptide cyclo(S,S)-N^a-acetyl-Cys-(N^a-methyl)Arg-Gly-Asp-Pen-NH₂ (Ali *et al.*, EP 0 341 915, whose disclosure is herein incorporated by reference in its entirety) and the peptide cyclo(S,S)-(2-mercaptophenyl)benzoyl-(N^a-methyl)Arg-Gly-Asp-(2-mercaptophenylamide (EP 0 423 212, whose disclosure is herein incorporated by reference in its entirety). Other fibrinogen antagonists useful in the present invention are those peptides disclosed by Pierschbacher *et al.*, WO 89/05150 (US/88/04403); Marguerie, EP 0 275 748; Adams *et al.*, U.S. 4,857,508; Zimmerman *et al.*, U.S. 4,683,291; Nutt *et al.*, EP 0 410 537, EP 0 410 539, EP 0 410 540, EP 0 410 541, EP 0 410 767, EP 0 410 833, EP 20 25 0 422 937 and EP 0 422 938; Ali *et al.*, EP 0 372 486; Ohba *et al.*, WO 90/02751 (PCT/JP89/00926); Klein *et al.*, U.S. 4,952,562; Scarborough *et al.*, WO 90/15620 (PCT/US90/03417); Ali *et al.*, PCT/US90/06514 and PCT/US92/00999; the peptide-like compounds disclosed by Ali *et al.*, EP 0 381 033 and EP 0 384 362; and the RGD peptide cyclo-N^a-acetyl-Cys-Asn-Dtc-Amf-Gly-Asp-Cys-OH (in which Dtc is 4,4'-dimethylthiazolidine-5-carboxylic acid and Amf is 4-aminomethylphenylalanine). 30

The RGD peptide may be usefully included in the microemulsion formulation in an amount up to about 400mg/g of the hydrophilic phase or from 0.1 to 40 mg/g of the formulation.

35

Other peptides useful in the present invention include, but are not limited to, other RGD containing peptides such as those disclosed by Momany, US 4,411,890 and US 4,410,513; Bowers *et al.*, US 4,880,778, US 4,880,777, US 4,839,344; and WO 89/10933 (PCT/US89/01829); the peptide Ala-His-D-Nal-Ala-Trp-D-Phe-Lys-NH₂ (in

which Nal represents β -naphthylalanine) and the peptides disclosed by Momany, US 4,228,158, US 4,228,157, US 4,228,156, US 4,228,155, US 4,226,857, US 4,224,316, US 4,223,021, US 4,223,020, US 4,223,019 and US 4,410,512.

5 Other suitable peptides include hexapeptides such as the growth hormone releasing peptide (GHRP) His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂, (Momany, US 4,411,890, the disclosure of which is herein incorporated by reference in its entirety). This may usefully be included in an amount up to about 250mg/g of the hydrophilic phase or from 0.1 to 25mg/g of the formulation.

10 Suitable larger polypeptides and proteins for use in microemulsions of the present invention include insulin, calcitonin, elcatonin, calcitonin-gene related peptide and porcine somatostatin as well as analogs and homologs thereof. Other suitable larger polypeptides include those disclosed by Pierschbacher *et al.*, US 4,589,881 (>30 residues); Bittle *et al.*, US 4,544,500 (20-30 residues); and Dimarchi *et al.*, EP 0 204 480 (>34 residues).

Other type of compounds useful in the present invention include analogs or homologs of LHRH which display potent LH releasing activity or inhibit the activity of LHRH; analogs or homologs of HP5 (hemopoietic factor 5) which possesses hematopoietic activity; 20 analogs or homologs of endothelin which possess hypotensive activity; analogs or homologs of enkephalin which have antinociceptive activity; analogs or homologs of chloreycystokinin; analogs or homologs of cyclosporin A which have immunosuppressive activity; analogs or homologs of atrial natriuretic factor; peptidergic antineoplastic agents; analogs or homologs of gastrin releasing peptide; analogs or homologs of somatostatin; 25 gastrin antagonists; bradykinin antagonists; neuropeptins antagonists; bombesin antagonists; oxytocin agonists and antagonists; vasopressin agonists and antagonists; hirudin analogs and homologs; analogs and homologs of the cytoprotective peptide-cyclolinopeptide; alpha MSH analogs; analogs, and homologs of MSH releasing factor (Pro-Leu-Gly-NH₂); peptides which inhibit collagenase; peptides which inhibit elastase, 30 peptides which inhibit renin; peptides which inhibit HIV protease; peptides which inhibit angiotensin converting enzyme; peptides which inhibit chymases and tryptases and peptides which inhibit blood coagulation enzymes.

Other suitable drugs include non-peptide therapeutic agents such as antibiotics, 35 antimicrobial agents, antineoplastic agents, cardiovascular and renal agents, antiinflammatory, immunosuppressive and immunostimulatory agents and CNS agents.

Preferably, the drug is a peptide such as a fibrinogen receptor antagonist peptide (an RGD peptide), GHRP (His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂), a vasopressin, a calcitonin or an

insulin, more preferably the fibrinogen receptor antagonist peptides cyclo(S,S)-N^α-acetyl-Cys-(N^α-methyl)Arg-Gly-Asp-Pen-NH₂ or cyclo(S,S)-(2-mercapto)benzoyl-(N^α-methyl)Arg-Gly-Asp-(2-mercapto)phenylamide or GHRP.

5 In a preferred aspect, the present invention provides compositions in the form of microemulsions comprising a peptide which may be orally administered and which will retain biological activity, thereby overcoming the disadvantages of earlier formulations in which the bioavailability of the peptide has been less than satisfactory. In particular, the present invention provides compositions which by their nature permit the preparation and
10 administration of a peptide in sufficiently high concentration to allow not only convenient oral administration but also adequate bioavailability of the peptide.

For a water-soluble drug, the degree of incorporation into the (w/o) microemulsions of the present invention is limited only by its solubility in the hydrophilic phase. By a person skilled in the art, isotonic aqueous phase in the physiological pH range (3 - 8) may be used to aid drug dissolution by the proper modification of the high HLB to the low HLB (free fatty acid) ratio, without compromising the integrity of the active ingredient and stability of the composition.

20 The aqueous hydrophilic phase suitably comprises water or an isotonic saline solution and may also include a pharmaceutically acceptable solvent which is non-miscible with the selected lipophilic phase, such as polyethylene glycol, propylene glycol, sorbitol, mannitol and other mono- or di-saccharides.

25 It will be readily appreciated by the skilled man that not all blends of an oil, low and high HLB surfactants and hydrophilic phase will yield stable, self-emulsifying microemulsions within the scope of the present invention. Appropriate ratios may, however, be readily determined by the skilled man with the aid of a phase diagram. For the purposes of illustration, the preferred system of a medium chain alkyl or dialkyl sulfate or sulfonate or
30 sulfosuccinate salt, a free fatty acid (first low HLB surfactant), an oil, a further, second, low HLB surfactant, and an aqueous solution will be considered. Although this system comprises five components, a pseudo-ternary phase diagram may be constructed by reducing the number of variables to three, by holding two pairs (free fatty acid/sulfate or sulfonate or sulfosuccinate salt and oil/second low HLB surfactant) each in a fixed ratio.
35 Each of the three variables may then be represented by one side of the triangle. Thus, in fig. 1, (1) represents the mixture of oil and second low HLB surfactant, at a fixed ratio X, (2) the hydrophilic (aqueous) phase and (3) the free fatty acid and sulfate or sulfonate or sulfosuccinate salt at a fixed ratio Y. By way of example, the point "A" represents a microemulsion of 40% oil plus second low HLB surfactant, 10% aqueous phase and 50%

free fatty acid plus sulfate or sulfonate or sulfosuccinate salt. It will be appreciated by the skilled man that if either the second low HLB surfactant or the free fatty acid is omitted, then the variables (1) or (3) will no longer need to be a fixed ratio and corresponding phase diagrams may be constructed.

5

The regions of the phase diagram in which microemulsions according to the present invention exist may be determined by titrating a mixture of the oil and second low HLB surfactant (in a fixed ratio) against the free fatty acid plus sulfate or sulfonate or sulfosuccinate salt (in a fixed ratio) and the hydrophilic phase, noting points of phase separation, turbidity and transparency. Clear, transparent compositions are indicative of the formation of a stable microemulsion. These compositions may then be plotted on the phase diagram, to generate a microemulsion field, the boundary of which represents the transition from clear, transparent compositions (microemulsions) to turbid compositions, as shown in figure 1.

10

Once stable transparent systems are obtained, simple tests, such as dye solubilization, dispersibility in water and conductivity measurements may be used to determine whether the microemulsion is an (o/w)- or a (w/o)-type. A water-soluble dye will disperse in an (o/w) microemulsion while it will remain in its original form in a (w/o) microemulsion.

15

Likewise, (o/w) microemulsions are generally dispersible in water whereas (w/o) microemulsions are generally not. In addition, (o/w) microemulsions conduct electricity whereas (w/o) do not. The isotropic nature of the system may be confirmed by examination thereof under polarised light. The microemulsions are isotropic and therefore non-birefringent when examined under polarised light.

20

Microemulsions within the scope of the present invention are those falling within the microemulsion existence field of the pseudo-ternary phase diagram.

25

Accordingly, the present invention provides compositions which form stable, self-emulsifying (w/o) microemulsions as hereinbefore defined in which the relative proportions of the various components lie within the microemulsion existence field of a pseudo-ternary phase diagram such as figure 1.

30

By this process of constructing a representative range of phase diagrams, for different ratios X and Y, it is possible to determine appropriate quantities of the various components which will lead to stable, self-emulsifying microemulsions falling within the present invention.

Suitably, the oil comprises from about 5 to 95, preferably from about 10 to 80% (w/w) of the microemulsion.

5 Suitably, the total low HLB surfactants comprises from about 15 to 85, preferably from about 20 to 70% (w/w) of the microemulsion.

Suitably, the total high HLB surfactant comprises from about 5 to about 75%, preferably about 5 to about 50%, more preferably from about 7.5 to about 30% (w/w) of the microemulsion.

10 Suitably the hydrophilic phase comprises from just greater than 0 to about 40%, preferably from about 0.1 to 20%, more preferably from about 0.1 to 10% and most preferably from about 1 to 5% (w/w) of the microemulsion.

15 It will be readily appreciated by the skilled person that, in general, if it is desired to accomodate a larger amount of hydrophilic phase, this will have to be matched by an increase in the relative amount of high HLB surfactant(s), at the expense of lipophilic components.

20 The oil and the second low HLB surfactant may be combined and mixed at various ratios. Useful (w/o) microemulsions which have relatively low viscosity throughout the whole of the microemulsion field may be obtained when the ratio of oil to second low HLB surfactant is in the range of about 5:1 to about 1.5:1, preferably about 4:1 to about 2:1. It is found that as the ratio of oil to second low HLB surfactant is increased towards 5:1, the 25 microemulsion field tends to shrink towards the apex of the phase diagram formed by the sides representing (1) and (3).

30 In preferred microemulsions, the free fatty acid and the fatty alkyl or dialkyl sulfate, or sulfonate, or sulfosuccinate salts are preferably present in the range of about 5 to about 75%, more preferably about 5 to about 50%, most preferably from about 7.5 to about 30% (w/w) of the microemulsion.

35 The microemulsions of the present invention are substantially non-opaque, that is they are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state, they are optically isotropic (non-birefringent) when examined under polarized light. They exhibit excellent stability at low and ambient temperatures, without phase separation, clouding or precipitation, even over prolonged periods of time. The formulations may be stored in a stable form at various temperatures, such as at 4°C, room temperature, 37°C and at 50°C, preferably at 4°C or room temperatures. On dilution with

excess aqueous phase, the microemulsions of the present invention tend to invert to (o/w) emulsions.

Preferably, the diameter of droplets or particles of the microemulsions of the present

5 invention, measured, for instance, as the number-average diameter by laser light scattering techniques, is less than 150 nm, more preferably less than 100 nm, yet more preferably less than 50 nm and most preferably in the range 5 to 35 nm.

The various phases may optionally contain, some in minor amounts, for instance less

10 than 3, preferably less than 1% (w/w), of further ingredients, such as, but not limited to:

- i) antioxidants such as n-propyl gallate, butylated hydroxyanisole (BHA) and mixed isomers thereof, d-a-tocopherol and mixed isomers thereof, ascorbic acid, propylparaben, methylparaben and citric acid (monohydrate);
- ii) stabilizers, such as hydroxypropyl cellulose;
- 15 iii) antimicrobials, such as benzoic acid (sodium salt);
- iv) protease inhibitors such as aprotinin.

The present invention includes not only microemulsions which are liquids or gels at room temperature (about 23°C) but also microemulsions which, while liquid at the body

20 temperature of the animal being treated, are solid at room temperature. Such solid microemulsions may be readily prepared by using a high melting oil and, optionally, a high melting low HLB surfactant. Suitable such oils or low HLB surfactants will have a melting point above room temperature, preferably above 30°C and examples thereof are well known in the art. Suitable high melting oils include hydrogenated coconut oil and

25 palm oil and blends thereof, such as the Hydrokote oils (available from Karlshamns Lipid Specialities), hydrogenated peanut oil and various hydrogenated vegetable oils. Also suitable are mixtures of triesters and diesters of propylene glycerol and lauric acid, such as the product Witespol H-15, available from Huls of Germany and which contains a 9:1 mixture of tri- and di-esters. Suitable high melting low HLB surfactants include safflower

30 oil monoglycerides such as the products MYVEROL 18-92 and 18-99.

The present invention may provide for microemulsions which, upon addition of aqueous fluid, convert to both O/W emulsions and microemulsions. In systems that convert to O/W microemulsions the aqueous phase is preferably a 10-95%, preferably a 20-70%, more preferably a 20-50% by weight solution of such compounds as sorbitol,

5 polyethylene glycol (PEG), mannitol, propylene glycol, mono- and di-saccharides and mixtures thereof.

The microemulsions of the present invention form spontaneously or substantially spontaneously when their components are brought into contact, that is without the

10 application of substantial energy supply, for instance in the absence of high shear energy such as imparted by homogenization and/or microfluidization or other mechanical agitation. Accordingly, the microemulsions may be readily prepared at room temperature by the simple process of admixing appropriate quantities, with gentle hand mixing or stirring, if necessary, to ensure thorough mixing. Preferably, the drug is dissolved in the
15 hydrophilic phase, either directly or by dilution of a stock solution thereof and this may then be added to a pre-mixed combination of the oil and, if being used, a second low HLB surfactant with mixing, followed by the fatty acid salt and, the free fatty acid and non-ionic high HLB surfactant or *vice versa*.. Alternatively, a drug-free microemulsion may be initially prepared by admixing the oil and surfactants and drug-free hydrophilic phase;
20 to which may then be added further hydrophilic phase in which the drug is dissolved. Microemulsions which are solid at room temperature may be prepared by using higher temperatures, such that the various components are all liquids, for instance between 40 and 60°C, to facilitate mixing. Such microemulsions may then be allowed to cool down to room temperature, during which solidification occurs.

25 Microemulsions of the present invention may be pharmaceutical compositions comprising a therapeutic agent and which may be given to animals, including man.

Accordingly, in a further aspect, the present invention provides a method of treatment
30 which comprises administering an effective amount of a pharmaceutical composition as hereinbefore defined to a patient in need thereof.

It will be appreciated by the skilled man that the amount of drug required for therapeutic effect will vary with the drug chosen, the nature and severity of the condition and the
35 animal undergoing treatment and is ultimately at the discretion of the physician. Furthermore, the optimal quantity and spacing of individual dosages of a drug will be determined by the nature and extent of the condition being treated, the form, route and site of administration, the particular patient being treated and that such optima can be determined by conventional techniques. It will also be appreciated that the optimal course

of treatment, that is, the number of doses given, may be readily ascertained using conventional course of treatment determination tests.

In a further aspect, the present invention provides for the use of an oil, a surfactant system
5 comprising a mixture of high and low HLB surfactants in which the high HLB surfactant
is an aliphatic, aryl or aliphatic aryl sulfate or sulfonate or sulfosuccinate salt admixed with
a medium chain fatty acid salt, and optionally admixed with a non-ionic high HLB
surfactant, a therapeutic agent and a hydrophilic phase, as hereinbefore defined, in the
manufacture of a medicament.

10 Pharmaceutical compositions of the present invention may be administered parenterally,
enterally or *via* a mucous membrane, for instance, by injection or by oral, topical, rectal,
colonic or intra-vaginal administration. Accordingly the compositions will be presented
15 in forms suitable for such. Thus for instance, pharmaceutical compositions intended for
oral administration may be presented in soft gelatin capsules while the viscosity
characteristics of some of the pharmaceutical compositions make them suitable for direct
topical application. Solid formulations are preferred for colonic and rectal administration.

20 The microemulsion compositions of the present invention without a drug are novel and
useful as precursors to drug-containing microemulsions. Accordingly, in a further aspect,
the present invention provides a composition comprising an oil; a surfactant system
comprising a mixture of high and low HLB surfactants in which the high HLB surfactant
is an aliphatic, aryl, aliphatic-aryl sulfate or sulfonate or sulfosuccinate salt, admixed with
a medium chain fatty acid salt, and optionally admixed with a non-ionic high HLB
25 surfactant and an aqueous hydrophilic phase which components on admixing form a
stable, self-emulsifying, water-in-oil (w/o) microemulsion.

The invention will now be illustrated by, but not limited to, the following descriptions
(drug-free compositions) and examples (drug-containing compositions).

30

DESCRIPTIONS

Description 1 - Phase Diagrams for Representative Compositions

35 Pseudo-ternary phase diagrams were constructed for the following representative systems,
with deionized water as the aqueous phase for all but description 4 which used saline:

Description	Oil/2nd low HLB surfactant	Ratio	Free fatty acid/fatty acid salt	Ratio	Fig.
1	CAPTEX 8000/ CAPMUL C8	2:1	Caprylic acid/ Dioctyl sodium sulfosuccinate (pure, USP100%)	3:1	2
2	CAPTEX 8000/ CAPMUL C8	2:1	Caprylic acid/ Dioctyl sodium sulfosuccinate surfactant, 15% sodium benzoate (85%)	3:1	3
3 a	MIGLYOL 808 Imwitor 308	2:1	Caprylic acid/ Dioctyl sodium sulfosuccinate (pure, USP 100%)	3:1	4
4 b	MIGLYOL 808 Imwitor 308	2:1	Caprylic acid/ Dioctyl sodium sulfosuccinate (pure, USP 100%)	3:1	5

a deionized water was used as aqueous phase

b aqueous phase: saline

5 By way of example, a pseudo-ternary phase diagram was constructed for the system comprising CAPTEX 8000 and CAPMUL C8 (ratio 2:1), caprylic acid and dioctyl sodium sulfosuccinate (ratio 3:1) and aqueous phase (saline or deionised water). The region of the phase diagram in which microemulsions were formed was determined by titrating a mixture of CAPTEX 8000 and CAPMUL C8 against a solution of caprylic acid and dioctyl sodium sulfosuccinate and saline, noting points of phase separation, turbidity and transparency.

10

The resultant phase diagram is shown as figure 2. A wide range of clear, transparent, liquid (w/o) microemulsions was available. These were stable at room temperature and 15 37°C. On dilution with excess aqueous phase, inversion to a turbid (o/w) emulsion was observed.

In a similar manner, phase diagrams were constructed for the other systems given in the table and these are shown as figs. 3 to 5. A similar range of microemulsion fields was

obtained. The microemulsions were found to have relatively low viscosity throughout the field. In addition, it was noted that when the aqueous phase was changed from deionized water to saline (description 4), lower levels of aqueous phase could then be accommodated, as anticipated from the ionic nature of the high HLB surfactant.

5

EXAMPLES

Examples 1-2 describe w/o microemulsions comprising CAPTEX 8000 and CAPMUL C8 (ratio 2:1); caprylic acid and dioctyl sodium sulfosuccinate (ratio 3:1) and an aqueous phase and either GHRP (His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂), MW at about 850 or RGD peptide (cyclo(s,s)-(2-mercapto)benzoyl-(N²-methyl)-Arg-Gly-Asp-(2-mercapto)-pheylamide, MW of about 650). The relative proportions are given in the following table:

Example	Drug	Drug conc. mg/g form.	CAPTEX 8000 & CAPMUL C8, %(w/w)	Na Dioctyl sulfosuc-cinate %(w/w)	aqueous phase %(w/w)
1	GHRP	3.0	65	30	5 ^a
2	RGD Peptide	3.0	65	30	5 ^b

15

Footnotes to table:

^a aq. = isotonic soln containing acetic acid and sodium chloride at pH 5.0;

^b saline.

20 These microemulsions were formulated by initially preparing the drug-containing hydrophilic phase, either by dissolving the appropriate amount of drug in the appropriate amount of the aqueous phase or, more preferably, using a stock solution which was then further diluted if so required, and with vortex stirring if necessary to obtain complete dissolution. The hydrophilic phase containing the drug was then added to the appropriate 25 amounts (by weight) of a mixture of the oil and the second low HLB surfactant, to which was then added a solution of dioctyl sodium sulfosuccinate in free fatty acid, with gentle stirring (magnetic hot plate stirrer). Alternatively, the hydrophilic phase containing the drug was added to the solution of dioctyl sodium sulfosuccinate in free fatty acid. This was mixed completely and then added to the oil plus second low HLB surfactant mixture. 30 If necessary, the drug-containing microemulsion was then diluted with the corresponding drug-free microemulsion to adjust the concentration of the drug.

BIOLOGICAL EXAMPLES

Bioavailability of Calcein

5 Using a standard unconscious rat model (Walker et al, Life Sciences 47, 29-36, 1990), the intraduodenal bioavailability of a model compound calcein (5(6)-carboxy-fluorescein, MW=623) when dosed as a microemulsion of any of the preceding Examples may be assessed and compared with that obtained when the same compound is dosed by the same route but as a solution in isotonic Tris buffer. The levels of the compound in the plasma

10 samples are determined using fluorescence spectroscopy. After an i.d. dosing at approximately a 1.25 μ Mol/kg or 1.0ml/kg microemulsion, the bioavailability is determined and compared to the bioavailability when administered as an isotonic Tris buffer.

15 The bioavailability determination as noted above, is a well recognized experiment to those of skill in the art, but is reiterated herein for convenience as follows:

Male rats which are fasted overnight when employed for the absorption studies. Intravenous (i.v.) or intraduodenal (i.d.) administration of the compound (in this instance Calcein) either from a solution of a microemulsion is carried out using conventional

20 methods.

For the i.v. administration, fasted rats are anesthetized with an intraperitoneal injection of a mixture of Rompun (5mg/kg) and Ketaset (35mg/kg) and a jugular catheter is implanted. Rats are allowed to recover from surgery for 1 day. Catherized rats were fasted for 18 hr prior to the administration of the compound. Each compound is

25 administered by lateral tail-vein administration. Blood samples of 0.5ml aliquots were collected at 0, 1, 3, 5, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. The 0 min sample is taken 15 min prior to administration of the dose. Plasma is removed from whole blood by centrifugation at 1600x g for 5 min, and then stored at -20C in 250 μ l aliquots per sample. The blood pellet is reconstituted with 12.5 units heparinized saline and returned

30 to the appropriate rat via the jugular catheter. After the experiment, rats are euthanized with i.v. administration of pentobarbital.

For i.d. administration, in addition to jugular catheters, duodenal catheters are surgically implanted in anesthetized rats and the animals allowed to recover from surgery for 4-5 days. The compound is administered either from a solution or microemulsion via

35 the duodenal catheter. Blood samples of 0.5 ml aliquots are collected via jugular catheter in heparinized eppendorf tubes at 0, 10, 30, 60, 120, 180, 240 and 1440 min. The 0 min sample is taken 15 min prior to administration of the dose. Plasma is collected for analysis and the blood returned to rats as described for i.v. administration protocol. The stool of each rat over time is evaluated for consistency by a rank of soft, soft/watery, or mucoid.

Upon termination of the absorption study (4-6, or 24 hrs post-dosing) the animals are euthanized with asphyxiation using carbon dioxide and exanguinated. An abdominal incision is then made and the entire GI tract removed and observed under a microscope at 50x magnification.

5 Plasma levels of Calcein are determined by fluorescence using a Perkin Elmer LS 50 luminescence spectrometer at excitation and emission wavelenghts of 490 and 515 nm respectively. The bioavailability (%F) is calculated from the AUC (area under the plasma concentration-time curve) following i.d. or i.v. dosing using the following equation:

$$\%F = (AUC_{id}/AUC_{iv}) \times (Dose_{iv}/Dose_{id}) \times 100$$

10

The formulations of the present invention may be tested for GI irritation assessment with and without an active ingredient by the following method:

Oral Dosing in Rats/GI Irritation Assessment

15 Suitable rats for use in this assement are male Sprague-Dawley (Caesarian Delivery - Virus Antibody Free; Charles River Laboratories). The rats are fasted overnight the day before the experiment. Dosing with the microemulsion at the desired dose is done by gavage at a volume not exceeding 10 ml/kg. Upon termination of the experiment animals are euthanized with asphyxiation using carbon dioxide and exsanguinated. Abdominal incisions are then performed and gross observations of the 20 gastric and duodenal mucosa are made with naked eyes and under a microscope (Nikon model SMZ-10 binocular microscope).

25 One aspect of the present invention are the formulations of w/o self-emulsifying microemulsions with or without peptide which produce little, if any, damage along the GI tract upon oral administration. The present formulations may be given orally by gavage (preferably at three rats per formulation). After 24 hrs the animals are exsanguinated and upon abdominal incisions are examined both by naked eye and under the microscope. The mucosal surface of both the stomach and duodenum of the animals are examined to see if they are free of any lesions at naked eye.

30 Oral Bioavailability of an RGD Peptide in Rats:

In the procedure described below microemulsions formulated as described above and containing, for instance, 3mg of a peptide, such as an RGD fibrinogen receptor antagonist containing peptide, per gr of microemulsion are tested in the following manner for oral bioavailability.

35

a) Intravenous (iv) administration of peptide in saline

Fasted rats are given an intraperitoneal (i.p.) injection and surgically fitted with femoral artery catheters. Rats ware allowed to recover from the surgery for 1 day.

Catherized rats are fasted for 18 hr prior to the experiment. Each rat receives 3mg of peptide by lateral tail-vein administration from a solution prepared as follows:

10.84 mg peptide q.s. to 8ml with 0.9% saline solution. Blood samples of 0.5ml aliquots are collected at 0, 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 minutes.

5 The 0 min. sample is taken 15 min prior to administration of the dose. Plasma is removed from the whole blood by centrifugation at 16000Xg for 5 min, and then plasma is stored at -20°C in 250 μ l aliquots per sample. The blood pellet is reconstituted with heparinized saline and returned to the appropriate rat via catheter. After the experiment, rats are euthanized with iv administration of pentobarbital.

10

b) Intraduodenal (i.d.) administration of peptide in microemulsion

Fasted rats are given an i.p. injection of anesthesia cocktail and surgically fitted with jugular and duodenal catheters. Rats are allowed to recover from the surgery for 4-5 days. Catherized rats are fasted 18-20 hrs. prior to the experiment. Each rat receives

15 10mg of peptide in either microemulsion or saline solution. Blood samples of 0.5ml aliquots are collected via jugular catheter in heparinized eppendorf tubes at 0, 10, 30, 60, 120, 180, 240 and 1440 minutes. The 0 min sample is taken 15 min prior to administration of the dose by duodenal catheter. Plasma is collected for analysis and the blood returned to rats as described in the i.v. administration (part a) above. After 1440
20 min, rats are euthanized by iv administration of pentobarbital, exsanguinated and the GI tract removed for gross observation.

c) Analysis of peptide plasma concentration

Standards are placed before and after the sample for HPLC analysis. A 50 μ l aliquot for 0-200 ng peptide, 25 μ l aliquot for 1000-2000 ng peptide, 15 μ l aliquot for 10,000 ng peptide and a 50 μ l aliquot of each sample is analyzed by post-column fluorescence detection. Fluorescence chromatography data is collected and integrated using a Nelson Chromatography Data System. The peak area ration (Y) and peptide standard concentration (X) are used to determine the slop of a line which is forced through the origin from the equation: slope = (sum of X*Y)/(Sum of X²). The slope represents the relationship between peak area ratio and peptide plasma concentration for the samples.

d) Calculation of Bioavailability

First, the area under the plasma concentration curve (AUC) from 0 to 240 minutes is determined for each rat. For id administration, percentage bioavailability is determined for each animal by the following equation with the average AUC from iv administration: $[(AUC_{id}/AUC_{iv})*(dose_{iv}/dose_{id})] * [100]$.

The oral bioavailability data for the RGD peptide in rats after intraduodenal administration of a microemulsion containing the above formulations incorporating a fibrinogen receptor antagonist of a peptide dose may then be obtained in the above noted manner.

5

When applicable, the formulations of the present invention are tested for *in vivo* activity. As one of the active ingredients utilized herein is a fibrinogen receptor antagonist a platelet aggregation assay is employed to determine pharmacological activity of the peptide from microemulsions. These studies are carried out as shown below.

10

Oral Dosing in Dogs/Platelet Aggregation Assay :

Dogs used in this assay are male Mongrels (i.e. from mixed breeds). The dog(s) are fasted overnight the day before the experiment. The cephalic vein of choice is prepared for the indwelling catheter in the following way: the area is first shaved and 15 cleaned with a gauze soaked in 70% alcohol. An indwelling catheter is placed in the cephalic vein and attached to a luer lock adapter filled with 3.8% sodium citrate. The catheter is securely taped down. When a blood sample is withdrawn, a 0.3 ml of blood is withdrawn into a separate 1 cc syringe before the actual sample so that dilution of the blood sample from the sodium citrate contained in the luer lock adapter is avoided. Then 20 2.7 ml of blood are drawn in a 3 cc syringe and placed in a Venoject vacuum tube containing 0.3 ml of 3.8% sodium citrate and labelled with the appropriate time point. The tube containing the blood sample in 3.8% sodium citrate is gently inverted few times to mix components and then 1 ml is withdrawn for the whole blood aggregation assay. The rest of the blood sample is transferred to an eppendorff tube and upon centrifugation 25 the supernatant plasma is removed and transferred to a new tube which is then frozen for subsequent HPLC analysis to determine peptide content.

Just after the zero time point blood sample is withdrawn, an appropriate dose of microemulsion with or without peptide is administered orally to the dog using a size 12 gelatin capsule.

30

The blood samples are then assayed for platelet aggregation inhibition using the Chromo-Log whole blood aggregometer. The instrument is warmed to 37°C before samples are run and the probe is cleaned with distilled water and a soft brush. The probe is attached to the aggregometer and placed in a cuvette of saline solution and warmed in a side cuvette well in the aggregometer. For the actual assay, 1 ml of the 2.7 ml of blood 35 sample mixed with the 0.3 ml 3.8% sodium citrate contained in the Venoject vacuum tube is added to a cuvette and placed in the aggregometer well. A stir bar is placed in the cuvette and set at 900 rpm. The probe is placed firmly into the test cuvette and the lid is shut. Baselines, zero and calibration are set. Calibration is set equal to 20 = 5 ohms. The stirring cuvette is permitted to settle for five minutes at which point 5 µl of collagen is

added to the whole blood that is being stirred to yield to a 5 μ g/ml final solution in the cuvette.

The reaction is monitored for two minutes once the slope change reaches the baseline of the collagen addition, calculating the change in ohms per minute using the 5 slope of the two minutes. The change in ohms per minute is calculated as a % of the control. The control value is determined by the average of the -15 and the 0 time points. After each use the probe is removed and cleaned with distilled water and wiped with a soft cloth and brush.

10 Discussion and Conclusion:

A dog is considered a good model to assess the pharmacological effect of one class of peptides of interest herein, the RGD containing fibrinogen receptor antagonists. Experiments are conducted as described above, with a peptide dose of 3 mg/kg or 15 microemulsion dose of 0.5 ml/kg. Control experiments where the peptide is given orally in a saline solution are independently carried out earlier and serve as a useful comparison to the effects seen with the microemulsion-formulated peptide.

As one of the active ingredients utilized herein is a Growth Hormone Releasing Peptide the appropriate assay for in vivo activity is determined as shown below.

20

In Vivo Testing of GHRP-Containing Microemulsion:

A microemulsion with a composition (w/w) in accordance with the Examples above is made. Upon preparation, they are further stored in a stable form at ambient temperature for approximately 48 hrs before the in vivo evaluation. A control solution of a GHRP 25 peptide, His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂, in saline at 1.5 mg/ml is also prepared.

30

Dosing is done by single intraduodenal administration of GHRP at 3 mg/kg in male rats in saline solution (control) and in the aforementioned microemulsion using 3 rats in each case. Prior to actual sampling and dosing, each rat is anesthetized with Pentobarbital at 50 mg/kg i.p., diluted with saline to a final volume of 1 ml. The rats stay anesthetized for the entire experiment. Dosing is achieved in the following way: a small incision 2-3 cm long is made on the abdominal midline, and then a purse-string suture is placed on the duodenal muscle. A small hole is made in the center of the purse-string suture in which a blunt 23 G stub needle attached to a tuberculin syringe is inserted to deliver the dose.

35

Upon completion of dosing, the purse-string is tied to close the opening. The incision is closed with wound clips. A 0.2 ml blood sample is obtained via jugular catheter at the following intervals: -15, 0, 5, 10, 15, 30, 45, 60, 90, and 120 minutes. Blood samples are stored on ice and subsequently analyzed for Growth Hormone by an RIA method.

Analysis of the samples generated from the experiment mentioned above need to have determined the pharmacological activity of GHRP. Positive data will indicate that Growth Hormone Releasing Peptide is orally active from the microemulsion formulation of the present invention. However, blood levels and actual bioavailability need to be 5 correlated to observed pharmacological activity.

The amount of active ingredient required for therapeutic systemic administration will, of course, vary with the compound chosen, the nature and severity of the condition, and the mammal, including humans, undergoing treatment, and is ultimately at the 10 discretion of the physician.

Ultimately, the present invention also includes a method of treatment which comprises administering an effective amount of a pharmaceutical composition as defined herein to a patient in need thereof. Preferably, the therapeutic agent is selected from a 15 fibrinogen receptor antagonist peptide, growth hormone releasing peptide or an analog or homolog thereof, a vasopressin or analog or homolog thereof, elcatonin, a calcitonin, a calcitonin-gene realeated peptide, a porcine somatostatin an analog or homolog thereof, insulin or a homolog or analog thereof. The disease states and uses of each of the aforementioned therapeutic agents, as well as the other therapeutic agents noted herein, 20 are well known to those of skill in the art. For many of these agents such use is already cross referenced in their respective patents, for instance, use as platelet aggregation inhibitor, a growth promoter, for the treatment of osteoporosis, and for the treatment of diabetes.

What we claim is:

1. A pharmaceutical composition comprising:
 - (a) an oil;
 - 5 (b) a surfactant system comprising a mixture of high and low HLB surfactants in which the low HLB surfactant is an admixture of:
 - i) a medium-chain or long chain free fatty acid; and
 - ii) a medium or long chain mono/di-glyceride or a sorbitan medium or long chain ester or mixtures thereof;
- 10 and the high HLB surfactant is:
 - iii) a sulfate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfate, an aryl sulfate, an aliphatic-aryl sulfate, or mixtures thereof;
 - iv) a sulfonate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfonate, or aryl sulfonate, an aliphatic-aryl sulfonate, or mixtures thereof;
 - 15 v) a sulfosuccinate or pharmaceutically acceptable salt thereof, which is an aliphatic sulfosuccinate, an aryl sulfosuccinate, an aliphatic-aryl sulfosuccinate, or mixtures thereof; or
 - vi) a mixture of any of iii), and/or iv), and/or v) above; andwherein the high HLB surfactant is optionally mixed with the salt of a medium or long chain free fatty acid and/or a nonionic high HLB surfactant;
- 20 (c) an aqueous hydrophilic phase; and
- (d) a water-soluble biologically active agent;

which on admixing form a stable, self-emulsifying, water-in-oil (w/o) microemulsion.

- 25 2. The composition according to claim 1 in which the oil comprises pharmaceutically acceptable fatty acid triglycerides, fatty acid diesters of propylene glycol, fatty acid esters of polyethylene glycol, or mixtures thereof.
- 30 3. The composition according to claim 2 in which the fatty acid triglyceride, fatty acid diester, and the fatty acid polyol ester comprises a medium-chain fatty acid moiety.
4. The composition according to claim 3 in which the fatty acid triglyceride or fatty acid diester comprises caprylic acid optionally admixed with capric acid moieties.
- 35 5. The composition according to claim 1 or 2 in which the high HLB surfactant is a medium-chain alkyl or di-alkyl sulfate, sulfonate, or sulfosuccinate or a salt thereof.

6. The composition according to Claim 5 in which the salt is a pharmaceutically acceptable water-soluble salt alkali metal salt, an ammonium or a quaternary ammonium salt or an amine.
- 5 7. The composition according to claim 5 or 6 in which the high HLB surfactant is dioctylsulfosuccinate or dodecyl sulfate or a salt thereof.
- 10 8. The composition according to claim 1 in which the low HLB surfactant is admixture comprises as a component a medium chain monoglyceride, a medium chain diglyceride or a mixture thereof.
9. The composition according to claim 8 in which the medium chain mono- and di-glycerides are formed from caprylic and capric acids.
- 15 10. The composition according to claim 9 which comprises from about 50 to 100% caprylic acid and from about 0 to 50% capric acid mono- and di-glycerides.
11. The composition according to claim 1 in which the free fatty acid is a medium chain fatty acid selected from caprylic acid, capric acid or a mixture thereof.
- 20 12. The composition according to claim 1 in which the low HLB surfactant comprises a blend of medium-chain fatty acid monoglycerides, medium-chain fatty acid diglycerides and medium-chain free fatty acids.
- 25 13. The composition according to any of claims 1 to 12 which optionally comprises the salt of a medium-chain fatty acid.
14. The composition according to claim 13 in which the high HLB surfactant is a medium-chain alkyl or dialkyl sulfate, sulfonate or sulfosuccinate or salt thereof.
- 30 15. The composition according to claim 13 in which the medium chain components are octyl, decyl, docecytl, or a mixture thereof.
16. The composition according to claim 1 in which the biologically active material is a therapeutic agent which is a peptide.
- 35 17. The composition according to claim 16 in which the peptide is a fibrinogen receptor antagonist peptide, a Growth Hormone Releasing Peptide, a vasopressin, a calcitonin or an insulin.

18. The composition according to claim 1 which comprises a high melting oil and/or a high melting low HLB surfactant, and which is solid at room temperature and liquid at body temperature.

5

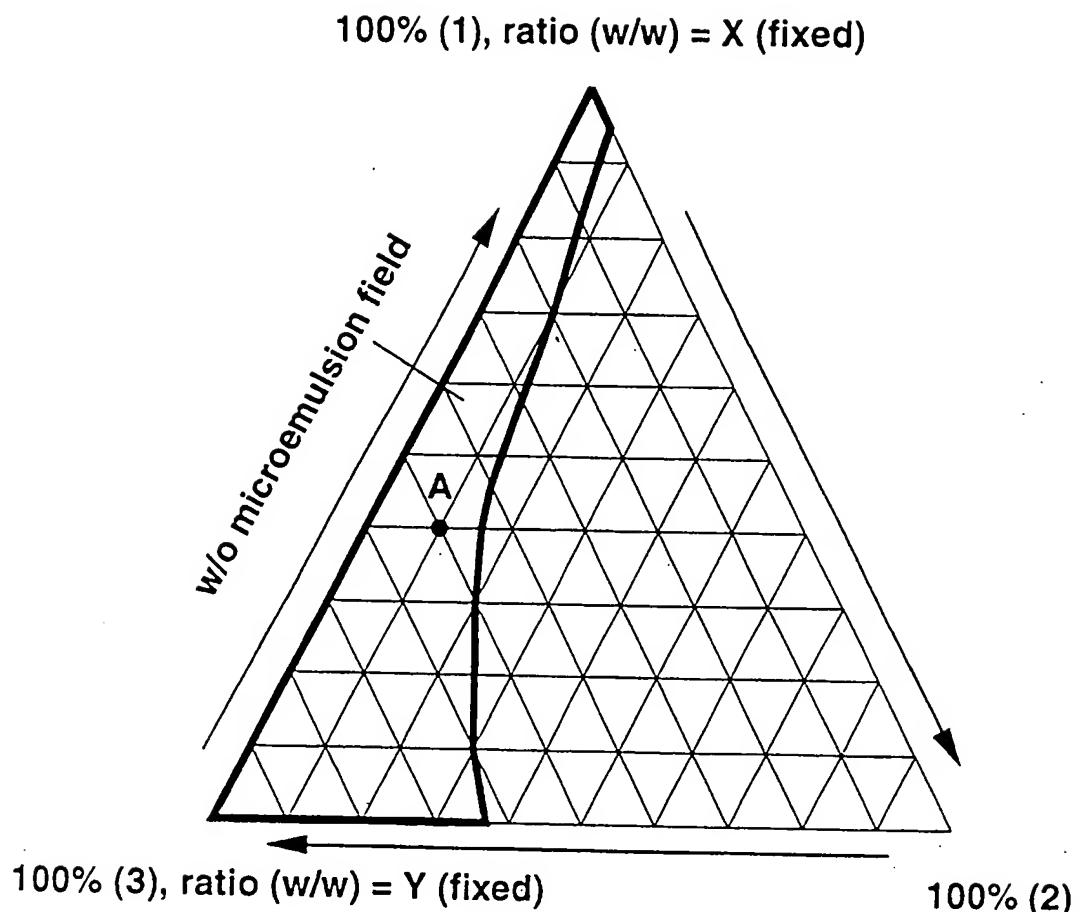
19. The composition according to claim 1 in which the relative proportions of the oil, surfactants and aqueous phase lie within the microemulsion existence field of the pseudo-ternary phase diagram of Figure 2.

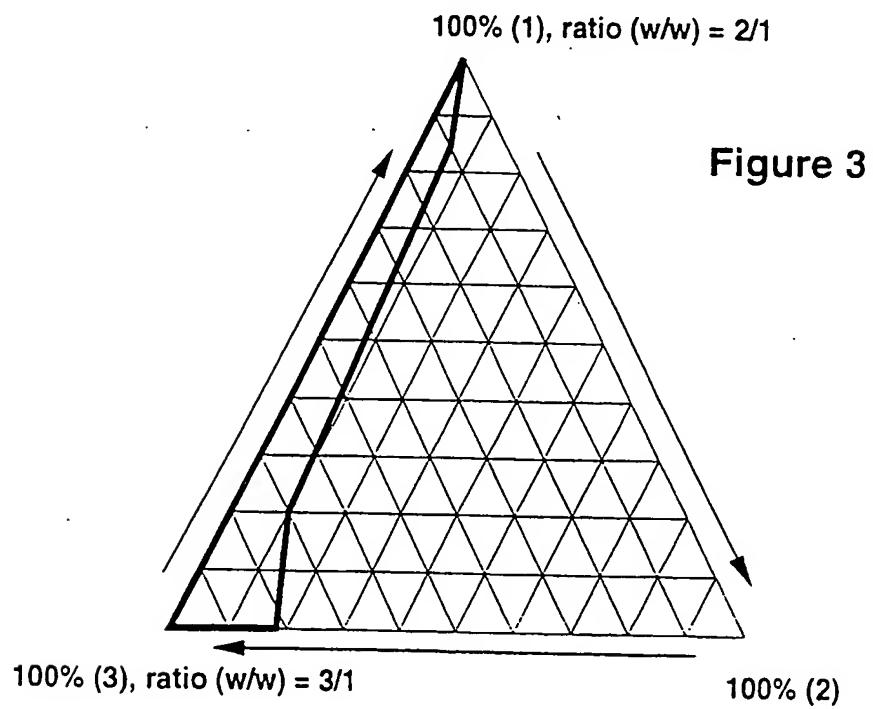
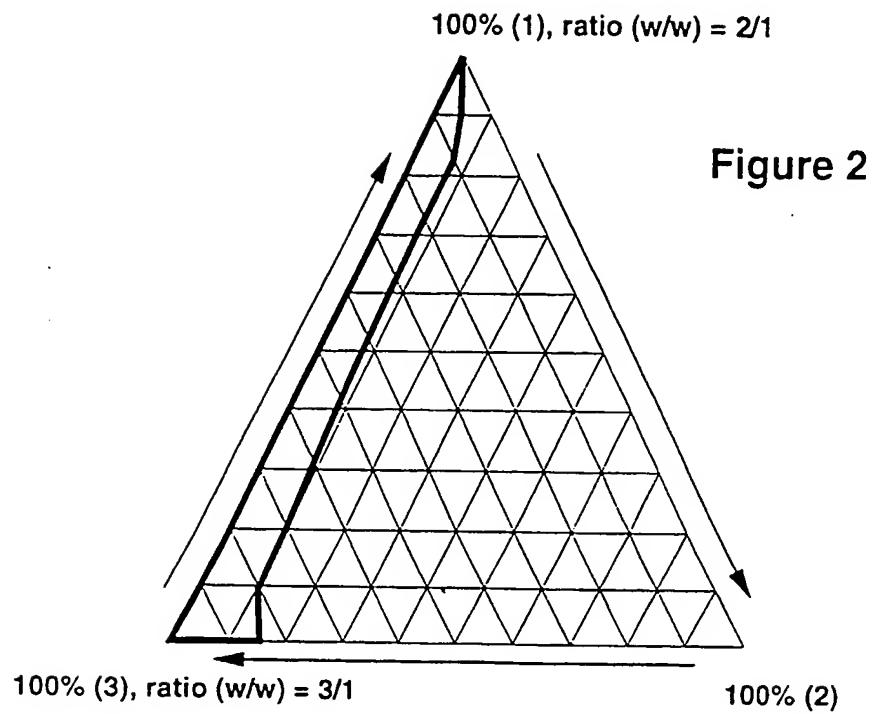
10 20. A method of treatment which comprises administering an effective amount of a pharmaceutical composition as defined in claim 1 to a patient in need thereof.

15 21. A composition as claimed in claim 1 wherein the aqueous hydrophilic phase comprises a 10-95% weight percent solution of sorbitol, polyethylene glycol, mannitol, propylene glycol, mono- and di-saccharides, and mixtures thereof.

22. A composition as claimed in claim 1 wherein the oil has a melting point above room temperature.

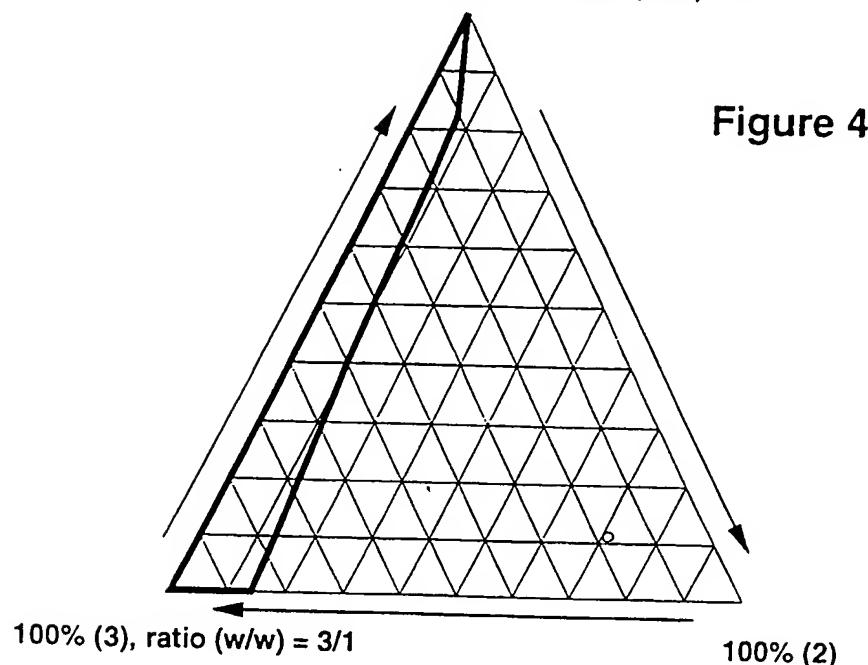
1/3

**Figure 1**

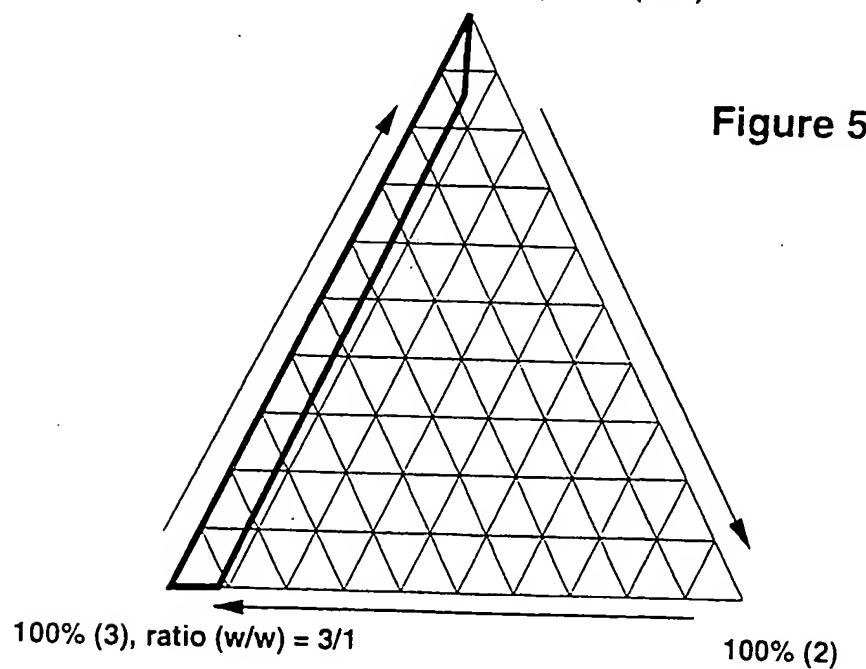


3/3

100% (1), ratio (w/w) = 2/1



100% (1), ratio (w/w) = 2/1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 37/02, 37/26, 9/22, 9/66

US CL : 424/450, 455, 460; 514/4, 12, 937, 938, 964

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450, 455, 460; 514/4, 12, 937, 938, 964

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	UK,A, 2,098,865 (JOACHIM) 01 DECEMBER 1982, SEE THE ENTIRE DOCUMENT, PARTICULARLY PAGE 2, LINES 19-58 AND PAGE 3, LINE 11 TO PAGE 4, LINE 25.	1-22
A	US,A, 4,963,367 (ECANOW) 16 OCTOBER 1990, SEE THE ENTIRE DOCUMENT.	1-22
A	DERWENT ABSTRACT C89-18822, ISSUED 22 DECEMBER 1988, "MULTIPHASE AQ. EMULSION COMPOSITE PRODN.-BY DISSOLVING E.G. PROPYLENE GLYCOL FATTY ACID ESTER IN OIL PHASE AND AQUEOUS PHASE, MIXING AND ADDING LECITHIN", SEE THE ABSTRACT.	1-22

 Further documents are listed in the continuation of Box C. See patent family annex.

•	Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A	document defining the general state of the art which is not considered to be part of particular relevance		
E	earlier document published on or after the international filing date	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O	document referring to an oral disclosure, use, exhibition or other means	*&*	document member of the same patent family
P	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

08 APRIL 1994

Date of mailing of the international search report

25 APR 1994

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